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Visit-to-Visit Blood Pressure Variability, Neuropathology, and Cognitive Decline

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Neurology® 2021;96:e2812-e2823. doi:10.1212/WNL.0000000000012065

Abstract

Objective

Large systolic blood pressure (SBP) variability has been proposed as a novel risk factor for dementia above and beyond SBP levels, but the underlying neuropathology is largely unknown. We investigated the relationship among visit-to-visit SBP variability, cognitive deterioration, and underlying neuropathologic changes.

Methods

We used longitudinal data (between 2005 and 2019) from the National Alzheimer's Coordinating Center. A total of 13,284 dementia-free participants ≥50 years of age were followed up over a median of 5.0 (interquartile range 3.1–7.6) years. Neuropathology data were available in 1,400 autopsied participants. Visit-to-visit SBP variability was quantified from repeated annual SBP measurements. Cognitive deterioration was defined as conversion from normal cognition to mild cognitive impairment (MCI) or dementia or from MCI to dementia.

Results

Larger visit-to-visit SBP variability was associated with cognitive deterioration (adjusted odds ratio comparing extreme quintiles 2.64, 95% confidence interval 2.29–3.04, $p < 0.001$). It was also associated with a higher burden of vascular pathology (including microinfarcts, white matter lesions, atherosclerosis of the circle of Willis, and arteriolosclerosis) and with neurofibrillary tangle pathology assessed by Braak staging (all $p < 0.05$). The association with cognitive deterioration and vascular pathology appeared stronger among those with normal cognition vs those with MCI at baseline. These findings were observed after adjustment for age, sex, mean SBP, and other confounding variables. Similar results were observed for diastolic blood pressure variability.

Conclusion

Larger visit-to-visit SBP variability was associated with cognitive deterioration. It was also associated with cerebrovascular pathology and neurofibrillary tangles. These results suggest the intertwined role of vascular and Alzheimer disease pathology in the etiology of dementia.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

Aβ = β-amyloid; **ACD** = Alzheimer's Disease Center; **AD** = Alzheimer disease; **BP** = blood pressure; **CDR** = Clinical Dementia Rating; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **CI** = confidence interval; **DBP** = diastolic BP; **MCI** = mild cognitive impairment; **NACC** = National Alzheimer's Coordinating Center; **OR** = odds ratio; **SBP** = systolic BP; **SOB** = Sum of Boxes.

Hypertension has been proposed as a major contributor to dementia, but the relationship between blood pressure (BP) and dementia is not completely understood.[1-3] Accumulating evidence demonstrates that visit-to-visit BP variability over months or years, which was previously perceived as random noise, may contribute to coronary heart disease, renal disease, stroke, and mortality above and beyond BP level.[4-6] It has also been reported that excessive visit-to-visit BP variability was associated with an elevated risk of dementia in older adults.[7,8] However, it remains unknown whether visit-to-visit BP variability contributes to dementia risk at an early cognitively normal stage, at a more advanced stage with cognitive impairment, or at both stages, the answer to which will inform the etiologically relevant window and guide the risk stratification and prevention of dementia.

Furthermore, despite increasing epidemiologic evidence linking visit-to-visit BP variability to dementia, the underlying neuropathologic changes are largely unknown. It has been suggested that excessive visit-to-visit BP variability contributes to white matter hyperintensities,[9] yet the association of visit-to-visit BP variability with other cerebrovascular pathologic changes that are commonly found at autopsy in dementia cases such as cerebral atherosclerosis and arteriolosclerosis[10] is undetermined. In addition, hypertension has been suggested to contribute to Alzheimer disease (AD) pathologies such as the deposition of intracellular tau tangles[11-13] and extracellular β-amyloid (Aβ) plaques.[12-15] It is unknown whether this is the case for the pathogenic role of visit-to-visit BP variability in the development of dementia. Therefore, we investigated the relationship among visit-to-visit BP variability, cognitive deterioration, and underlying neuropathologic changes using longitudinal data from the Alzheimer's Disease Research Centers Program of the National Institute on Aging through the National Alzheimer's Coordinating Center (NACC) database.

Methods

Study Population

This study included participants from the longitudinal study of the NIH–National Institute on Aging–supported Alzheimer's Disease Centers (ADCs), a nationwide consortium of academic research sites (alz.washington.edu/WEB/studypop.html). We used data collected from 39 past and current ADCs across the United States between June 2005 and August 2019, with details described elsewhere.[16] In this study, we included participants ≥50 years of age who were free of clinically diagnosed dementia at the initial visit and completed BP measurements from at least 3 visits. Ultimately, 13,284 participants met the criteria. Autopsy permission was obtained according to applicable state laws. Of 2,331 participants who died during the follow-up, 1,400 (60%) had brain autopsy and were included in neuropathology analysis (figure 1 shows the flowchart).

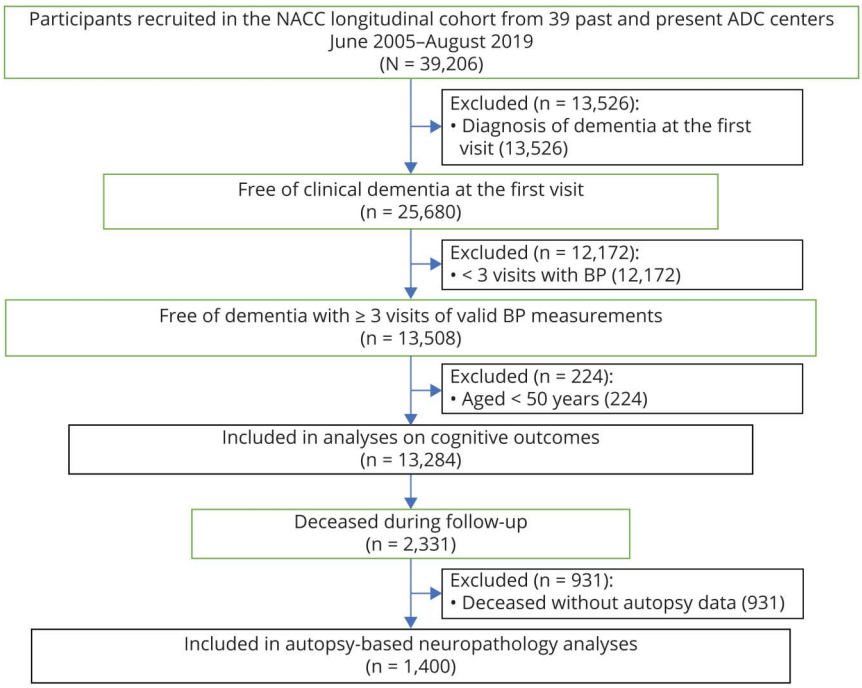
Visit-to-Visit BP Variability Assessment

One BP reading was recorded at each approximately annual visit in the sitting position following the NACC standard protocol.[17] Each participant contributed to ≥3 BP measurements, and the median number was 5 (interquartile range 4–7) per person. Visit-to-visit BP variability was defined as the root mean square error from the linear regression of longitudinal BP readings on the participant's age (in years) at BP measurement. This measure captures BP variability (in millimeters of mercury) that is independent of the rate of change in BP (i.e., slope of the linear regression) over time. We primarily assessed visit-to-visit variability in systolic BP (SBP) because of its stronger association with adverse health outcomes.[18] We also repeated the analyses for diastolic BP (DBP). In addition, we assessed visit-to-visit SBP variability using the coefficient of variation, the commonly used metric.

Cognitive Assessment

Cognitive status was determined at each approximately annual visit by either a consensus team or a physician after a detailed examination and review of all available information according to standard research criteria as operationalized for the ADC program (alz.washington.edu/WEB/dataforms_main.html). Participants were classified as having normal cognition, impaired but not MCI (those who did not meet MCI criteria but were not judged to be cognitively normal, typically because of subjective cognitive decline but normal neuropsychological testing, sometimes vice versa), mild cognitive impairment (MCI), or a diagnosis of all-cause dementia. Because only 825 (6.5%) participants were initially classified as impaired but not MCI, we grouped it with the MCI category. Our primary outcome was the conversion of cognitive status across longitudinal visits. Given the multifaceted etiology of dementia, we focused on all-cause dementia. Specifically, participants who met either of the 2 following criteria were classified as having cognitive deterioration: progression from normal cognition at baseline to either MCI or dementia and progression from MCI at baseline to dementia during the follow-up. We also assessed cognitive deterioration using the Clinical Dementia Rating (CDR) Dementia Staging Instrument, specifically using the CDR Scale Sum of Boxes (SOB) score that was quantified approximately annually.[19]

Figure 1 Flowchart of the Study Population



ADC = Alzheimer's Disease Center; BP = blood pressure; NACC = National Alzheimer's Coordinating Center.

Neuropathologic Assessment

Autopsy-based neuropathology was assessed by trained neuropathologists using consensus guidelines, with in-depth data collection instruments described on the NACC website (alz.washington.edu/WEB/forms_np.html) and elsewhere.[20] In the current study, we explicitly analyzed cerebrovascular pathology and AD pathology using the NACC-derived variables (if available) that were harmonized across different form versions to facilitate an efficient analysis among all the participants. For cerebrovascular pathology, we examined the presence or absence of infarcts and lacunes (a harmonized composite of large cerebral artery infarcts, small artery ischemic and hemorrhagic lesions, and infarcts visible on gross examinations), microinfarcts (in cortical and subcortical regions), hemorrhages, and microbleeds. We also examined the severity of atherosclerosis in the circle of Willis, arteriolosclerosis (in subcortical white or gray matter regions), overall cerebral amyloid angiopathy, and white matter lesions, which were scored semiquantitatively as none, mild, moderate, or severe. Among them, white matter lesions were assessed only since 2014 (version 10) and were available for 825 participants. AD pathology was assessed with the ABC scoring system.[21] Specifically, the Thal phase for Aβ plaques (i.e., A score) classifies amyloid deposition throughout the encephalon as A0 (phase 0), A1 (phases 1 and 2), A2 (phase 3), or A3 (phase 4 and 5) stages, and it was included since 2014 (version 10). The Braak stage score classifies neurofibrillary tangle degeneration as B0 (stage 0), B1 (stages 1 and 2), B2 (stages 3 and 4), or B3 (stages 5 and 6). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score classifies neuritic plaque density semiquantitatively as none, sparse, moderate, or frequent.[22] We reclassified all these pathologies into 2 or 3 categories as appropriate to facilitate an easier interpretation.

Covariate Assessment

Data on demographic characteristics, *APOE* ε4 carrier status, smoking habits, body mass index, medical history (such as history of hypertension and diabetes), and current antihypertensive medication use (taken within the previous 2 weeks) were collected according to the NACC's Uniform Data Set data collection protocol.[23] These variables could potentially confound the association of visit-to-visit BP variability with cognitive function and underlying neuropathologic changes and were accounted for in the multivariable models described below.

Statistical Analysis

We analyzed the relationship among visit-to-visit BP variability, neuropathology, and cognitive deterioration in the following steps. We first assessed the association of visit-to-visit BP variability with cognitive deterioration. We then investigated the relationship between visit-to-visit BP variability and neuropathologic measures and between neuropathologic measures and cognitive deterioration. More details for each step are given below.

Association of Visit-to-Visit BP Variability With Cognitive Deterioration

We estimated the association of visit-to-visit BP variability with cognitive deterioration using logistic regression models

Table 1 Participant Characteristics

Characteristics	Overall (N = 13,284)	Neuropathology Analysis		
		Yes (n = 1,400)	No (n = 11,884)	*p* Value
Age at first visit, y	72 ± 9	80 ± 8	72 ± 8	<0.001
Age at death, y[a]	87 ± 8	87 ± 8	86 ± 8	<0.001
Women, %	59.8	51.5	60.8	<0.001
White, %	81.2	94.5	80.0	<0.001
Higher education (>16 y), %	61.5	60.9	61.6	0.59
Body mass index, kg/m^2	27.3 ± 5.2	26.1 ± 4.5	27.5 ± 5.2	<0.001
SBP, mm Hg	134 ± 18	136 ± 19	134 ± 18	<0.001
DBP, mm Hg	75 ± 10	73 ± 10	75 ± 10	<0.001
Antihypertensive treatment at baseline, %	53.4	63.4	52.2	<0.001
Antihypertensive treatment during the study, %	70.6	81.6	69.3	<0.001
APOE ε4 carrier (≥1 ε4 alleles), %	31.2	32.5	31.1	<0.001
Cognitive status at first visit				<0.001
Normal cognition, %	65	54.9	66	—
MCI, %	35	45.1	34	—
Cognitive status at final visit, %				<0.001
Normal cognition	55.9	31.6	58.8	—
MC	24.0	22.2	25.9	—
Dementia,	20.0	46.2	15.3	—
Past or current smoker, %	43.0	45.6	42.7	0.10
History of hypertension, %	69.0	78.2	67.9	<0.001
History of diabetes, %	12.1	11.2	12.2	0.10
History of cardiovascular disease, %	11.2	19.1	10.3	<0.001
History of stroke or TIA, %	5.2	9.6	4.6	<0.001
Cerebrovascular and AD pathology, %				
Presence of microinfarcts	—	26.3	—	—
Presence of infarcts and lacunes	—	20.1	—	—
Severe white matter lesions (n = 825)[b]	—	56.4	—	—
Atherosclerosis of circle of Willis (none, mild or moderate, severe)	—	15.4/69.8/14.8	—	—
Arteriolosclerosis (none, mild or moderate, severe)	—	18.1/70.0/11.9	—	—
Presence of hemorrhages and microbleeds	—	7.2	—	—
Cerebral amyloid angiopathy (none, mild or moderate, severe)	—	45.1/46.4/8.5	—	—
Thal phase for Aβ plaques (A0-1, A2, A3) (n = 889)[b]	—	31.4/41.1/27.5	—	—
Braak stage for neurofibrillary tangles (B0-1, B2, B3)	—	29.2/36.4/34.4	—	—
Density of neocortical neuritic plaques (no, sparse, moderate or frequent)	—	28.4/19.4/52.2	—	—

Abbreviations: Aβ = β-amyloid; AD = Alzheimer disease; DBP = diastolic blood pressure; MCI = mild cognitive impairment; SBP = systolic blood pressure.
Data are shown as mean ± SD and percentage for characteristics at initial visit unless otherwise specified.
[a] Applies only to the 2,331 participants who died during the follow-up, out of which 1,400 had available neuropathology data.
[b] Available only for a subset of ≈800 participants whose neuropathologic data were collected using the version 10 form since 2014.

Table 2 Association of SBP Visit-To-Visit Variability With Cognitive Deterioration

	ORs for cognitive deterioration by quintile of visit-to-visit SBP variability						Continuous visit-to-visit SBP variability	
	Quintile 1[b]	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*p* Value for trend	Per SD	*p* Value
All participants (n = 13,284)								
Events/participants, n	667/2,630	734/2,631	812/2,630	874/2,631	941/2,630	—	—	—
OR[a] (95% CI)	1.00	1.54 (1.34, 1.77)	2.04 (1.78, 2.35)	2.43 (2.11, 2.79)	2.64 (2.29, 3.04)	<0.001	1.36 (1.30, 1.42)	<0.0001
Subgroup with normal cognition at initial visit (n = 8,629)[c]								
Events/participants, n	267/1,578	349/1,710	384/1,736	478/1,786	511/1,738	—	—	—
OR[a] (95% CI)	1.00	1.53 (1.27, 1.85)	1.96 (1.62, 2.37)	2.53 (2.10, 3.05)	2.83 (2.34, 3.43)	<0.001	1.37 (1.30, 1.46)	<0.0001
Subgroup with MCI at initial visit (n = 4,655)[c]								
Events/participants, n	400/1,052	385/921	428/894	396/845	430/892	—	—	—
OR[a] (95% CI)	1.00	1.55 (1.27, 1.90)	2.14 (1.74, 2.63)	2.27 (1.84, 2.81)	2.38 (1.92, 2.95)	<0.001	1.33 (1.24, 1.42)	<0.0001

Abbreviations: CI = confidence interval; MCI = mild cognitive impairment; OR = odds ratio; SBP = systolic blood pressure.
[a] ORs were estimated with adjustment for age, sex, mean blood pressure, rate of change in blood pressure, antihypertensive medication use, education level, *APOE* genotype, smoking habits, weight status, history of diabetes, baseline Clinical Dementia Rating Sum of Boxes score, and the years of follow-up.
[b] Reference level.
[c] *p* Value for interaction between initial cognitive status and SBP variability was 0.078.

with adjustment for potential confounding variables including age, sex, education level, *APOE* ε4 carrier status, smoking habits, weight status, history of diabetes, baseline CDR-SOB score, antihypertensive medication use during the study, and the years of follow-up. We also adjusted for mean BP and rate of change per year (i.e., annual change) in BP to estimate the association with visit-to-visit BP variability that is independent of usual BP level and its change over time. We assessed BP variability on both continuous and quintile-based categorical scales. Testing for linear trends across quintiles of BP variability was performed by entering a single ordinal term in the models. We also stratified these analyses by initial cognitive status (i.e., normal cognition or MCI). In addition, to examine cognitive deterioration on a continuous spectrum, the rate of change (i.e., slope) in longitudinal CDR-SOB score across quintiles of visit-to-visit BP variability was estimated with a multivariate-adjusted linear mixed model to account for the correlation of within-participant repeated measurements. The model includes BP variability, age at BP measurement, their interaction term, and potential confounding variables, including mean BP, estimated annual change in BP, education level, APOE ε4 carrier status, smoking habits, weight status, history of diabetes, and antihypertensive medication use during the study. Both the intercept and the slope were included as random effects to account for the interindividual difference in baseline CDR-SOB and its rate of change over time. The coefficient of the interaction term estimated the difference in the rate of cognitive decline between groups with different levels of BP variability.

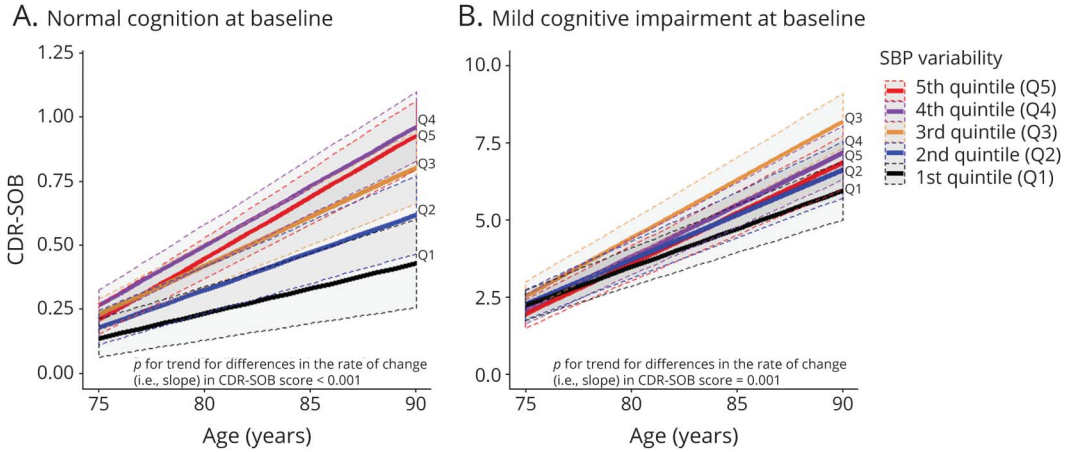
Association of Visit-to-Visit BP Variability With Neuropathology

The association of visit-to-visit BP variability with individual neuropathologic measures was estimated with multivariable logistic regression models with adjustment for age, sex, mean BP, education level, APOE ε4 carrier status, smoking habits, weight status, and history of diabetes, as well as mean BP, rate of change (per year) in BP, and antihypertensive medication use during the study. For neuropathologic measures with >2 categories, multinomial logistic regression was used. In addition, for individual vascular pathology measures that were associated with visit-to-visit BP variability, we derived a summary score of these measures (i.e., microinfarcts, white matter lesions, atherosclerosis of the circle of Willis, and arteriolosclerosis) by summing the scores for the presence (1 = presence, 0 = absence) or severity (none = 0, 1 = mild/moderate, and 2 = severe) of these markers. This summary score (0–6 points) reflects the overall BP variability–associated cerebrovascular burden and was used in subsequent analyses. We assessed the association of BP variability with several individual neuropathology measures without adjustment for multiple comparisons. These analyses may be interpreted as exploratory in nature, although the analyses were based on a priori hypotheses.

Association of Neuropathology With Cognitive Deterioration

Similarly, for neuropathologic measures that were associated with visit-to-visit BP variability in the above analyses, their association with cognitive deterioration was assessed by

Figure 2 Trajectory in CDR-5OB Score by Quintile of SBP Variability Among Participants With (A) Initial Normal Cognition and (B) Mild Cognitive Impairment



Predicted longitudinal trajectories in Clinical Dementia Rating Sum of Boxes (CDR-SOB) scores were obtained from linear mixed models with the adjustment for potential confounders, including age, sex, mean systolic blood pressure (SBP), and traditional vascular risk factors as specified in the text. Predicted longitudinal trajectories in CDR-SOB scores were plotted with covariates set at median levels of the study population. Shadows and dashed lines of the same color represent the 95% confidence intervals.

multivariable logistic regression with adjustment for age, sex, mean BP, education level, *APOE* ε4 carrier status, smoking habits, weight status, history of diabetes, baseline CDR-SOB score, and the years of follow-up. Analysis was conducted for the individual neuropathologic measures and the derived summary score of vascular pathology separately.

Secondary and Sensitivity Analyses

To allow a more integrated understanding of the role of both SBP level and SBP variability in cognitive deterioration, we also analyzed the association of mean SBP during follow-up with cognitive deterioration and neuropathology measures. Specifically, we present the associations without considering visit-to-visit SBP variability (model 1) and with additional adjustment for visit-to-visit SBP variability (model 2).

To examine potential effect modification, we stratified the analyses for cognitive deterioration by baseline age, sex, and antihypertensive medication use during the study. To assess the potential impact of measurement error on our main results, we additionally performed the analyses restricting to participants with at least 4, 5, and 6 annual BP measurements.

The proportion of missing data was small (ranging from 0%–8.6% for all the covariates analyzed), and missing data were handled using the missing indicator approach by adding an additional category indicating missing values. All effect estimates are given with corresponding 95% confidence intervals (CIs). All p values presented are 2 sided, with a value of $p \leq 0.05$ considered statistically significant. Statistical analyses were performed with SAS version 9.4 (SAS Institute Inc, Cary, NC) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was obtained from all participants at each ADC and approved by the ADC's Institutional Review Board.

Data Availability

NACC has developed and maintains a longitudinal database of standardized clinical and neuropathologic research data collected from the National Institute on Aging–funded ADCs across the United States. NACC data are freely available to all researchers.

Results

Of 13,284 participants who met our eligibility criteria, 7,949 (59.8%) were women, and the mean (SD) age at first visit was 72 (9) years. Table 1 provides the characteristics of all the participants and the subset with neuropathologic data. Over a median follow-up of 5.0 (interquartile range 3.1–7.6) years, with 5 completed visits on average, 1,409 (10.6%) cognitively normal participants progressed to MCI and 605 (4.6%) progressed to dementia, while 2,065 (15.5%) progressed from MCI to dementia. Among the 1,400 participants with neuropathologic data, the corresponding numbers of cognitive deterioration were 193 (13.8%), 174 (12.4%), and 473 (33.8%), respectively. Participants with neuropathologic data were older, had a higher proportion of men and White individuals, and had lower body mass index, higher SBP, lower DBP, and generally worse health profiles.

Visit-to-Visit SBP Variability and Cognitive Deterioration

As shown in table 2, higher visit-to-visit SBP variability was associated with cognitive deterioration from normal cognition

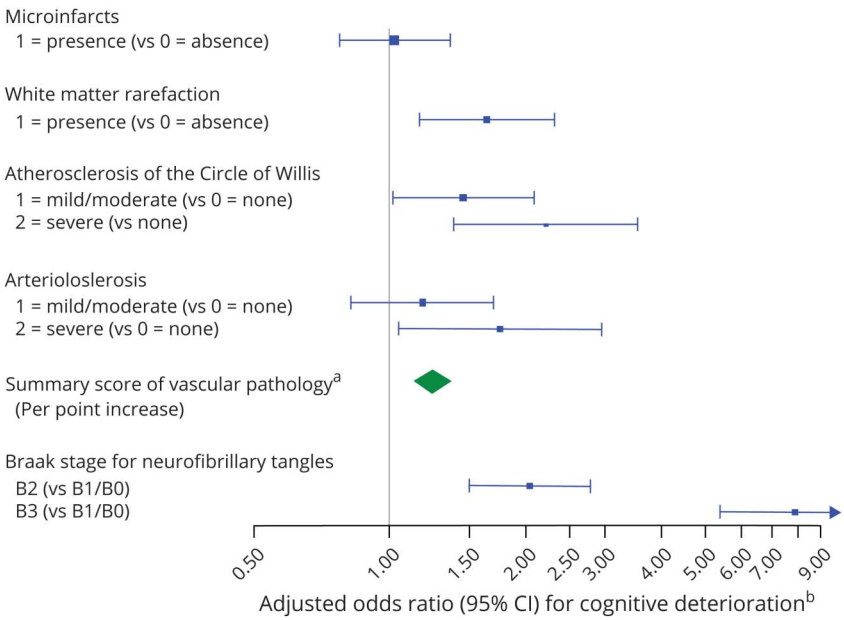
Table 3 Association of Visit-to-Visit SBP Variability With Neuropathology

Outcomes	ORs by Quintile of visit-to-visit SBP variability (95% CI)[a]					
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*p* for Trend
Cerebrovascular pathology						
Microinfarcts[b]						
Presence (vs absence)	1 (ref)	1.53 (1.01, 2.32)	1.41 (0.92, 2.14)	1.57 (1.04, 2.37)	1.64 (1.09, 2.49)	0.036
Infarcts and lacunes						
Presence (vs absence)	1 (ref)	1.24 (0.79, 1.95)	1.32 (0.84, 2.08)	1.42 (0.91, 2.21)	1.08 (0.68, 1.71)	0.610
White matter lesions[b]						
Presence (vs absence)	1 (ref)	1.85 (1.13, 3.05)	1.75 (1.08, 2.85)	1.99 (1.22, 3.25)	2.00 (1.22, 3.27)	0.017
Atherosclerosis of the circle of Willis[b]						
Mild/moderate (vs none)	1 (ref)	1.64 (1.01, 2.66)	1.34 (0.84, 2.12)	1.24 (0.78, 2.00)	1.57 (0.92, 2.67)	0.254
Severe (vs none)	1 (ref)	2.48 (1.25, 4.90)	1.54 (0.78, 3.05)	1.96 (1.01, 3.81)	2.85 (1.42, 5.73)	0.015
Arteriolosclerosis[b]						
Mild/moderate (vs none)	1 (ref)	1.19 (0.74, 1.92)	1.26 (0.78, 2.02)	1.07 (0.67, 1.72)	1.18 (0.71, 1.95)	0.675
Severe (vs none)	1 (ref)	1.59 (0.75, 3.41)	2.23 (1.08, 4.62)	1.96 (0.95, 4.04)	2.15 (1.01, 4.56)	0.047
Hemorrhages and microbleeds						
Presence (vs absence)	1 (ref)	1.48 (0.76, 2.90)	0.97 (0.47, 1.97)	0.94 (0.46, 1.93)	1.10 (0.54, 2.24)	0.681
Cerebral amyloid angiopathy						
Mild/moderate (vs none)	1 (ref)	1.48 (1.02, 2.14)	1.12 (0.78, 1.63)	1.18 (0.81, 1.71)	1.10 (0.75, 1.60)	0.919
Severe (vs none)	1 (ref)	1.59 (0.75, 3.37)	1.89 (0.94, 3.83)	2.17 (1.08, 4.37)	1.47 (0.69, 3.13)	0.186
AD pathology						
Thal phase for amyloid plaques (A score)						
A1 (vs A0)	1 (ref)	0.96 (0.55, 1.67)	0.80 (0.46, 1.40)	0.81 (0.46, 1.40)	0.88 (0.51, 1.53)	0.531
A2/A3 (vs A0)	1 (ref)	1.02 (0.52, 1.99)	1.32 (0.69, 2.50)	1.26 (0.66, 2.40)	1.29 (0.67, 2.50)	0.342
Braak stage for neurofibrillary tangles (B score)[b]						
B2 (vs B1/B0)	1 (ref)	1.16 (0.75, 1.79)	1.35 (0.87, 2.10)	1.73 (1.11, 2.69)	1.71 (1.09, 2.69)	0.004
B3 (vs B1/B0)	1 (ref)	1.43 (0.91, 2.24)	1.47 (0.94, 2.30)	1.67 (1.05, 2.66)	1.87 (1.16, 3.01)	0.009
Density of neocortical neuritic plaques (CERAD)						
Sparse (vs no)	1 (ref)	1.38 (0.83, 2.28)	1.09 (0.65, 1.84)	1.27 (0.76, 2.13)	1.09 (0.64, 1.85)	0.884
Moderate/frequent (vs no)	1 (ref)	1.09 (0.72, 1.64)	1.03 (0.69, 1.56)	1.17 (0.77, 1.77)	1.14 (0.75, 1.74)	0.477

Abbreviations: AD = Alzheimer disease; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CI = confidence interval; OR = odds ratio.
[a] With adjustment for age, sex, mean blood pressure, rate of change in blood pressure, antihypertensive medication use, education level, *APOE* genotype, smoking habits, weight status, and history of diabetes.
[b] *p* Value for trend < 0.05.

to MCI or dementia and from MCI to dementia after adjustment for age, sex, mean SBP, and other potential confounding factors (overall odds ratio [OR] comparing extreme quintiles 2.64, 95% CI 2.29–3.04; OR per 1-SD increase in SBP variability 1.36, 95% CI 1.30–1.42). The association was somewhat more pronounced among those with normal cognition at baseline compared to those with MCI (*p* for interaction = 0.078). A steeper slope of CDR-SOB score was also observed with higher visit-to-visit SBP variability for both cognitively normal participants and participants with MCI at baseline, with more consistent patterns observed for cognitively normal participants (*p* for interaction < 0.001; figure 2). Consistent association was also observed when SBP variability was quantified by coefficient of variation. The association did not differ significantly between participants who took antihypertensive medication and those who did not (*p* for

Figure 3 Association of Neuropathology Measures With Cognitive Deterioration



CI = confidence interval. [a]Only neuropathology measures that were significantly associated with systolic blood pressure (SBP) variability were assessed. Summary score of vascular pathology was derived by summing the presence (0 = absence and 1 = presence) or severity (0 = none, 1 = mild/moderate, 2 = severe) of these neuropathology measures, including microinfarcts, white matter rarefaction, atherosclerosis of the circle of Willis, and arteriolosclerosis. [b]Cognitive deterioration was defined as conversion from normal cognition to mild cognitive impairment (MCI) or dementia, or from MCI to dementia. Covariates adjusted in the multivariable logistic models include age, sex, mean SBP, education level, *APOE* ε4 carrier status, smoking habits, weight status, history of diabetes, baseline Clinical Dementia Rating Sum of Boxes score, and the years of follow-up.

interaction = 0.17). The results also remained similar when the analyses were restricted to participants with at least 4, 5, and 6 BP measurements. Consistent results were also observed for visit-to-visit DBP variability (data available from Dryad, tables S1–S3: doi.org/10.5061/dryad.kd51c5b4v).

Visit-to-Visit SBP Variability and Neuropathology

As shown in table 3, larger visit-to-visit SBP variability was associated with a higher burden of vascular pathology, including microinfarcts, white matter lesions, atherosclerosis of the circle of Willis, and arteriolosclerosis (all p for trend < 0.05) but not with cerebral infarcts and lacunes, hemorrhages and microbleeds, or cerebral amyloid angiopathy. Larger visit-to-visit SBP variability was also associated with neurofibrillary tangle pathology assessed by the Braak score (OR of B2 stage [vs B1/B0] comparing extreme quintiles of visit-to-visit SBP variability 1.71, 95% CI 1.09–2.69; OR of B3 stage 1.87, 95% CI 1.16–3.01). Visit-to-visit SBP variability was not associated with plaque pathology as assessed by the Thal phase for Aβ plaques or CERAD score. In addition, the association of visit-to-visit SBP variability with vascular pathology appeared to be stronger among those with normal cognition (vs MCI) at baseline (data available from Dryad, table S4: doi.org/10.5061/dryad.kd51c5b4v).

Neuropathology and Cognitive Deterioration

Cognitive deterioration in relation to SBP variability–associated neuropathologic measures is summarized in figure 3. Higher odds of cognitive deterioration were observed with severe white matter lesions (OR 1.64, 95% CI 1.17–2.32), atherosclerosis at the circle of Willis (OR 2.22, 95% CI 1.39–3.54), and arteriolosclerosis (OR 1.75, 95% CI 1.05–2.94) but not with microinfarcts. Consistent association was also observed for the sum score of these vascular pathologies. A remarkably strong association with cognitive deterioration was observed for more advanced stages of neurofibrillary tangles with an odds ratio (B3 vs B0/B1 stages) of 7.88 (95% CI 5.39–11.5). These associations appeared to be more pronounced among participants with normal cognition at baseline (data available from Dryad, figure S1: doi.org/10.5061/dryad.kd51c5b4v).

Secondary Findings on SBP Level

A higher SBP level was associated with overall cognitive deterioration after adjustment for potential confounding factors (model 1), although the magnitude of the association appeared less consistent than that for visit-to-visit SBP variability. This association was attenuated substantially and no longer statistically significant after further adjustment for visit-to-visit SBP variability (table 4). Compared to the association of SBP variability with neuropathology, mean SBP demonstrated overlapping yet distinct association patterns with neuropathology measures. A higher level of SBP was associated with increased burdens of microinfarcts, atherosclerosis of the circle of Willis, hemorrhages, and microbleeds, as well as higher density of neocortical neuritic plaques as assessed by CERAD score (all p values < 0.05), but not with white matter lesions, arteriolosclerosis, or neurofibrillary tangles (table 4).

Discussion

Our study, based on a longitudinal study of dementia-free older adults, found that higher visit-to-visit SBP variability was

Table 4 Association of Mean SBP Level With Cognitive Progression and Neuropathology

Outcomes	Model 1[a]			Model 2 (adjustment for SBP variability)[b]		
	OR (per 10–mm Hg increase in SBP)	OR (per 1-SD increase in SBP)	*p* Value	OR (per 10–mm Hg increase in SBP)	OR (per 1-SD increase in SBP)	*p* Value
Overall cognitive progression	1.04 (1.01, 1.08)	1.06 (1.01, 1.10)	0.011	1.00 (0.97, 1.04)	1.00 (0.96, 1.05)	0.840
Cerebrovascular pathology						
Microinfarcts[c]						
Presence (vs absence)	1.18 (1.08, 1.29)	1.25 (1.11, 1.41)	<0.001	1.17 (1.06, 1.28)	1.23 (1.08, 1.40)	<0.001
Infarcts and lacunes						
Presence (vs absence)	1.09 (0.98, 1.20)	1.12 (0.98, 1.28)	0.103	1.08 (0.97, 1.20)	1.11 (0.97, 1.28)	0.143
White matter lesions						
Presence (vs absence)	1.07 (0.96, 1.20)	1.10 (0.94, 1.28)	0.225	1.05 (0.93, 1.18)	1.07 (0.91, 1.25)	0.422
Atherosclerosis of the circle of Willis[c]						
Mild/moderate (vs none)	1.20 (1.07, 1.36)	1.28 (1.09, 1.51)	0.003	1.19 (1.05, 1.35)	1.27 (1.07, 1.50)	0.005
Severe (vs none)	1.48 (1.27, 1.73)	1.70 (1.38, 2.09)	5E-07	1.44 (1.22, 1.68)	1.63 (1.31, 2.02)	<0.001
Arteriolosclerosis						
Mild/moderate (vs none)	1.06 (0.95, 1.19)	1.08 (0.93, 1.26)	0.315	1.04 (0.92, 1.17)	1.05 (0.90, 1.23)	0.519
Severe (vs none)	1.13 (0.97, 1.32)	1.18 (0.95, 1.46)	0.128	1.08 (0.92, 1.28)	1.11 (0.89, 1.39)	0.338
Hemorrhages and microbleeds[c]						
Presence (vs absence)	1.29 (1.11, 1.50)	1.41 (1.16, 1.72)	7E-04	1.33 (1.14, 1.55)	1.47 (1.20, 1.80)	<0.001
Cerebral amyloid angiopathy						
Mild/moderate (vs none)	1.03 (0.94, 1.12)	1.04 (0.92, 1.17)	0.513	1.04 (0.95, 1.13)	1.05 (0.93, 1.18)	0.446
Severe (vs none)	1.15 (0.99, 1.34)	1.21 (0.99, 1.49)	0.064	1.15 (0.98, 1.34)	1.20 (0.97, 1.49)	0.094
AD pathology						
Thal phase for amyloid plaques (A score)						
A1 (vs A0)	1.06 (0.94, 1.21)	1.09 (0.92, 1.29)	0.33	1.06 (0.93, 1.21)	1.08 (0.91, 1.29)	0.362
A2/A3 (vs A0)	1.15 (0.99, 1.32)	1.20 (0.99, 1.46)	0.063	1.13 (0.97, 1.31)	1.17 (0.96, 1.43)	0.114
Braak stage for neurofibrillary tangles (B score)						
B2 (vs B1/B0)	1.04 (0.94, 1.16)	1.06 (0.92, 1.22)	0.427	1.00 (0.90, 1.11)	1.00 (0.87, 1.16)	0.979
B3 (vs B1/B0)	1.10 (0.99, 1.22)	1.14 (0.98, 1.31)	0.080	1.07 (0.96, 1.20)	1.10 (0.95, 1.27)	0.203
Density of neocortical neuritic plaques (CERAD)[c]						
Sparse (vs no)	1.00 (0.89, 1.13)	1.00 (0.85, 1.18)	0.955	1.00 (0.88, 1.13)	1.00 (0.85, 1.18)	0.997
Moderate/frequent (vs no)	1.15 (1.05, 1.27)	1.21 (1.06, 1.38)	0.004	1.15 (1.04, 1.27)	1.20 (1.05, 1.38)	0.007

Abbreviations: AD = Alzheimer disease; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CI = confidence interval; OR = odds ratio.
[a] Model 1 was adjusted for age, sex, antihypertensive medication use, education level, *APOE* genotype, smoking habits, weight status, and history of diabetes (as well as baseline Clinical Dementia Rating Sum of Boxes score and the years of follow-up when cognitive deterioration was the outcome).
[b] Model 2 was further adjusted for the rate of change in blood pressure and visit-to-visit systolic blood pressure variability in addition to model 1.
[c] *p* Value for trend < 0.05.

associated with cognitive deterioration after adjustment for potential confounding, including mean SBP level. The association appeared stronger among participants with normal cognition at baseline. Visit-to-visit SBP variability was also associated with both cerebrovascular pathology and neurofibrillary tangles. A similar association was observed for visit-to-

visit DBP variability. These findings suggest the potential role of visit-to-visit BP variability in the pathogenesis of dementia. This study also indicates the intertwined role of vascular and AD pathology in the multifactorial etiology of dementia.

Our study strengthens observations from population-based cohorts that linked higher BP variability to higher dementia risk.[7,8,24] It adds evidence, showing more pronounced associations observed in those with normal cognition than in those with MCI. This finding suggests the importance of targeting modifiable risk factors for dementia early to achieve effective protection. Our study also provides evidence linking visit-to-visit BP variability to postmortem neuropathology, suggesting the potential pathogenic role of visit-to-visit BP variability not only in a wide range of cerebrovascular pathologic changes but also in neurofibrillary tangle formation. The relationships among greater visit-to-visit BP variability, a higher burden of atherosclerosis of the circle of Willis, and cognitive deterioration were consistent with evidence linking systematic atherosclerosis to excessive visit-to-visit BP variability[25] and dementia.[26] Consistent associations were observed for white matter lesions and subcortical arteriolosclerosis, in concert with data showing cerebral small vessel disease as a major contributor to dementia.[27] While the strong association between visit-to-visit BP variability and neurofibrillary tangle pathology may appear surprising, it concurs with several lines of evidence linking hypertension to tau pathology.[11-13,28]

In addition, the associations of BP variability with cognitive deterioration and neuropathology were observed after accounting for mean BP level. The association of BP level per se with cognitive deterioration was not statistically significant, consistent with the main body of evidence showing attenuated or even reversed association of BP level in late life with dementia risk,[3,29,30] which suggests the inadequacy of BP level alone in capturing hypertension-related dementia risk in older populations. Neuropathologic changes associated with elevated BP levels were also partly different from those with BP variability. For example, higher SBP level was associated with hemorrhages and microbleeds, while increased SBP variability was associated with higher burdens of white matter lesions and arteriolosclerosis. Higher SBP level was associated with higher density of neuritic plaques, while larger SBP variability was associated with neurofibrillary tangles. These observations strengthen the speculation that visit-to-visit BP variability may capture excessive dementia risk and underlying neuropathologic changes in addition to conventional BP levels, which needs to be tested in future studies.

Little is known regarding the underlying mechanisms through which visit-to-visit BP variability may increase dementia risk; our study provides several clues. First, in line with previous reports,[7,8,31] the association of visit-to-visit BP variability with cognitive deterioration was observed in both the presence and absence of antihypertensive treatment, suggesting a potential pathogenic role of visit-to-visit BP variability unexplained by medication mismanagement. Second, we observed the association of visit-to-visit BP variability with several ischemia-related cerebrovascular lesion, such as microinfarcts, white matter lesions, arteriolosclerosis, and atherosclerosis, suggesting that increased visit-to-visit BP variability may cause brain ischemia and thereby cognitive decline. For example, large visit-to-visit BP variability may expose cerebral vessel walls to wider pressure fluctuation, especially when the cushioning function of large vessels is impaired, as occurs with arterial stiffness and atherosclerosis.[32,33] This chronic stress on vessel walls further contributes to chronic hypoperfusion, small vessel lesions, and impaired blood-brain barriers, thereby increasing the risk of dementia.[34] Third, the somewhat surprising link between visit-to-visit BP variability and neurofibrillary tangle pathology has several possible explanations. On the one hand, the relationship could be causal, and visit-to-visit SBP variability may lead to tau pathology through hypertension-related tau pathology,[11-13] which is not captured by mean SBP alone. For example, it may induce brain ischemia and blood-brain barrier dysfunction, which further contribute to the formation of neurotoxic molecules and the deposition of neurofibrillary tangles containing tau proteins.[35] On the other hand, reverse causation is also possible, and, for example, BP variability could be a preclinical marker of dementia if neurodegenerative changes of prodromal dementia, which affect neural regulation of BP, occur long (e.g., >1 decade) before the clinical manifestation of dementia.

Whether neuropathologic measures serve as potential mediators or effect modifiers in the relationship between BP variability and cognition warrants discussion. The vascular pathologic changes quantified through postmortem assessment could reflect chronic insults resulting from large BP variability, as discussed above, which further contribute to the etiology of dementia as mediators in the causal pathway linking visit-to-visit BP variability to cognition. Alternatively, postmortem neuropathology measures may reflect neuropathologic changes that had occurred before BP assessment and could therefore modify the relationships between BP variability and cognition if preexisting neurodegenerative changes affect the central regulation of BP. Because postmortem neuropathologic measures quantified the neuropathologic changes accumulated over the life course, we have limited ability to infer from the postmortem examination the timing of these neuropathology changes. It is thus possible that vascular and AD pathology could be mediators or effect modifiers in the relationship between BP variability and dementia. These hypotheses may be addressed by the use of premortem neuroimaging assessment of vascular and AD pathology in future investigation.

In addition, there is limited evidence on how BP variability could be modified to prevent or slow down the development of dementia if the causal relationship is established. A systematic review of trials of antihypertensive medication suggests that calcium channel blockers and nonloop diuretics could reduce visit-to-visit BP variability in addition to their effect on lowering BP level.[36] Several observational studies have also reported that large visit-to-visit BP variability was

associated with lifestyle factors such as a poorer diet, less education, less physical activity, higher body mass index, and higher fasting glucose level.[37-39] One interventional study suggests that dietary intervention in combination with physical exercise training may lower ambulatory BP variability and improve endothelial capacity.[40] Nevertheless, most of these data were from observational or nonrandomized intervention studies; thus, confounding bias is possible. Data from well-designed randomized controlled trials are needed to test whether elevated BP variability and related early vascular dysfunction can be targeted and reversed through pharmacologic or lifestyle modifications.

Several limitations warrant specific discussion. First, only 1 BP reading was recorded at each annual visit, making visit-to-visit BP variability prone to substantial measurement error. Nevertheless, we observed a consistent association of both visit-to-visit SBP and DBP variability with cognitive deterioration, using different indices in the overall sample and in the subset with neuropathology data, suggesting a robust association of visit-to-visit BP variability with dementia. Second, although NACC is one of the few longitudinal studies with valuable autopsy-based neuropathology, a few vascular neuropathology measures such as microinfarcts were assessed differently across visits, and the quality also varied across centers. This may introduce nondifferential misclassification that may have attenuated the true associations with cerebrovascular pathology. Third, because visit-to-visit BP variability spanning years was assessed simultaneously with cognitive deterioration and because we cannot infer from postmortem neuropathology the exact timing of pathologic changes, the temporal order of the observed relationships was unclear. Thus, alternative hypotheses such as neuropathology as a primary driver of both excessive visit-to-visit BP variability and dementia risk are possible. Our hypothesized causal relationships should therefore be further tested. Finally, our study is based on a longitudinal volunteer cohort comprising participants with a high level of educational attainment who joined the cohort due to various reasons such as concerns about family history and their own memory, and the findings should be replicated in population-based cohorts.

Increased visit-to-visit BP variability is associated with cognitive deterioration, as well as a higher burden of cerebrovascular pathology and neurofibrillary tangle pathology. These findings suggest the intertwined role of vascular and AD pathology in the etiology of dementia. Further studies are needed to clarify the temporal order of the relationships among BP variability, neuropathology, and dementia and to test whether the observed associations are causal.

Acknowledgment

The NACC database is funded by National Institute on Aging/NIH grant U01 AG016976. NACC data are contributed by the National Institute on Aging–funded ADCs: P30 AG019610 (principal investigator [PI] Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P30 AG062428-01 (PI James Leverenz, MD) P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P50 AG047266 (PI Todd Golde, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P30 AG062421-01 (PI Bradley Hyman, MD, PhD), P30 AG062422-01 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Thomas Wisniewski, MD), P30 AG013854 (PI Robert Vassar, PhD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P30 AG062429-01(PI James Brewer, MD, PhD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P30 AG062715-01 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), and P50 AG047270 (PI Stephen Strittmatter, MD, PhD).

Study Funding

This work was partly supported by American Heart Association grant 20POST35120057 (Dr. Ma) and P-30 grant P30AG062421 (Drs. Sudeshna Das, Blacker, and Hyman).

Disclosure

All authors report no disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* July 30, 2020. Accepted in final form March 5, 2021.

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Appendix *(continued)*

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Sudeshna Das, PhD	Massachusetts General Hospital, Harvard Medical School, Boston	Data analysis; drafted the manuscript for intellectual content
Albert Hofman, MD, PhD	Harvard T.H. Chan School of Public Health, Boston	Designed and conceptualized study; drafted the manuscript for intellectual content

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